

**REMARKS**

Claims 1, 3-4, 8, 11-21 and 24-27 currently appear in this application. The Office Action of January 7, 2005, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

**Rejection sunder 35 U.S.C. 112**

Claims 1, 2, 5, 8, 11-13, 18, 19, 21 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

This rejection is respectfully traversed. Claim 1 has now been amended to delete the proviso which was allegedly not described in the specification as filed.

Claims 1, 2, 5, 8, 11-13, 18, 19, 21 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as ebbing indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. Claim 1 has been amended to delete the limitation "X<sub>1</sub> and X<sub>2</sub> are not a hydrogen atom at the same time." Claims 25-27 have been amended to depend from claim 1.

**Double Patenting**

Claim 5 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1.

The present amendment cancels claim 5.

Art Rejections

Claims 1, 2, 5, 8, 11-13, 18, 19, 21 and 24-27 are rejected under 35 U.S.C. 102(b) over Grunwell et al.

This rejection is respectfully traversed. The Examiner asserts that formula (1) in claim 1 does not eliminate the prior art compound because the art recognizes the dashed line in the recited formula as an optional saturation, such as a double bond. However, this is not justified, as it is because of a misunderstanding.

In the previously filed amendment, the dashed line in formula (1) of claim 1 was deleted to limit the optional saturation to a single bond. Thus, the compounds of the present application represented by formula (1) do not clearly overlap with those of Grunwell et al., which have one or two double bonds in the lower left two fused six-membered rings. It is respectfully submitted that a dashed line no longer exist in formula (1) of the present application.

As stated by the Examiner, Grunwell et al. disclose a process for preparing a steroid having 4-ene or 5-ene, and teach that a 4,6-diene steroid is subjected to 1,6-alkyl addition reaction to obtain the corresponding 5-ene steroid which readily undergoes acid or base isomerization to form the corresponding 4-ene steroid (please refer to column 3, line 45 to column 4, line 12). However, Grunwell et al. do not disclose that a saturated ketone is produced by the process disclosed therein. In fact, a saturated ketone cannot be obtained by the process disclosed by Grunwell et al. It is clear from common knowledge in the art that a further chemical

reaction such as a reduction reaction of a 4- or 5-ene steroid is required for obtaining a saturated ketone.

It is respectfully submitted, therefore, that the compounds of the present invention, which are saturated ketones, are clearly distinguished from the unsaturated ketones disclosed by Grunwell et al., and it cannot be said that the former compounds have properties similar to the latter ones.

Claims 1, 2, 5, 8, 11-13, 18, 19, 21 and 24-27 are rejected under 35 U.S.C. 102(b) over Pierdet et al.

This rejection is respectfully traversed. In the previous amendment, claim 1 was amended to eliminate the dashed line, so that the compounds claimed herein are all saturated ketones. As stated by the Examiner, Pierdet et al. disclose a process for preparing a steroid having a 4-ene. However, there is nothing in Pierdet et al. that discloses or suggests that a saturated ketone is produced by the process described therein. In fact, a saturated ketone cannot be produced by the process of Pierdet et al., as one skilled in the art recognizes that a further chemical reaction such as a reduction reaction of a 4-ene steroid is required for obtaining a saturated ketone.

It is respectfully submitted, therefore, that the compounds of the present invention, which are saturated ketones, are clearly distinguished from the unsaturated ketones disclosed by Pierdet et al., and it cannot be said that the former compounds have properties similar to the latter ones.

Claims 1, 2, 5, 8, 11-13, 18, 19, 21 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by DeLaminat et al.

This rejection is respectfully traversed. Claim 1, and therefore the claims dependent therefrom, has been amended to delete "optionally" and to incorporate the limitations of claim 2 into claim 1 so that  $R^1$  is a group selected from the definition of  $R^{1a}$ . Additionally,  $Q^{17}$ ,  $Q^{22}$  and  $Q^{70}$  have been deleted from the definition of Q. It is respectfully submitted that claim 1, and the claims dependent therefrom, is not anticipated by DeLaminat et al.

Claims 1, 2, 5, 8, 11-13, 18, 19, 21 and 24-27 are rejected under 35 U.S.C. 103(a) over Grunwell et al.

This rejection is respectfully traversed. Grunwell et al. teach that an enormous number of 4-ene-androstane derivatives have some biological properties, including anabolic, androgenic and estrogenic and other hormonal properties, in addition to antitumor properties. Furthermore, the 4-ene-androstane derivatives are useful in the treatment of prostatic hypertrophy (refer to column 3, lines 58-70 and column 9, line 75 to column 10, line 16).

Grunwell et al. also teach that an enormous number of 5-ene-androstane derivatives have some biological properties, such as anabolic, androgenic, claudogenic, progestational, and anti-progestational activities (column 1, lines 14-16 and column 9, lines 62-75). In addition, the 5-3n3-androstane derivatives are useful as anti-fertility agents (column 9, lines 50-55) and show both progestation and anti-progestational activity (column 9, lines 57-61).

However, Grunwell et al. neither teach nor suggest that 4-ene-androstane derivatives or 5-ene-androstane derivatives are useful as anti-androgenic agents and pure antagonists. In addition, as noted above, the compounds of Grunwell et al. exhibit an androgenic property, namely, and agonistic action. Additionally, some of the 5-ene-androstane derivatives have both progestational and anti-progestational activity, namely, both agonistic and antagonistic action.

In contrast with the compound of Grunwell et al., the compounds of the present invention have only an anti-androgenic activity without showing an androgenic activity. This property is opposite that of the compounds of Grunwell et al. Therefore, the compounds of the present invention are quite different from those of Grunwell et al., and certainly could not be considered to be obvious in view of Grunwell et al. because of the completely different properties of the compounds.

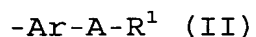
Additionally, the compounds of the present invention differ from those of Grunwell et al. in terms of the way the substituents are defined for each chemical formula.

In view of the foregoing facts, it would be difficult for one skilled in the art to expect that the compounds of the present invention have the same properties as those of Grunwell et al., and it has been demonstrated that the compounds of the present invention do indeed have quite different properties from the Grunwell et al. compounds.

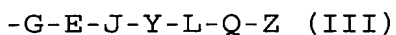
As explained above, unsaturated ketones are clearly different from saturated ketones because of differing chemical properties. In the first place, the compounds of the present

invention differ from those of Grunwell et al. in the steroid scaffold. In other words, the scaffold of the compounds of the present invention does not have 4-ene, and the compounds of the present invention are limited to an androstane scaffold. The compounds of the present invention differ from those disclosed by Grunwell et al. in the scaffold as well as in the positions and types of substituents. More specifically, the compounds of Grunwell et al. not only have a substituents in the 7-position, but also various other substituents in other position. In the working examples of Grunwell et al., only alkyl groups having 1 to 3 carbon atoms are disclosed. In addition, at column 9, lines 47-49, Grunwell et al. state that the corresponding 7 $\alpha$ -methyl derivatives are said to be particularly useful.

In contrast thereto, the compounds of the present invention have a characteristic substituent in the 7-position, namely, a substituents represented by formula (II):



wherein Ar represents a single bond or an aromatic hydrocarbon group, A represents a methylene group or -O-, R<sup>1</sup> represents a substituted alkyl group, a substituted alkenyl group, a substituted alkynyl group, and R<sup>1</sup> is R<sup>1a</sup> where R<sup>1a</sup> is the general formula (III):



wherein G, E, J, Y, L, Q AND Z are as defined in claim 2. These characteristic substituents could not have been conceived by one skilled in the art reading Grunwell et al., in which the substituents are limited to lower alkyl groups.

Grunwell et al. do not provide any working examples of "an antagonist which does not act as an agonist", and, furthermore, Grunwell et al. do not disclose or even suggest

such an antagonist. In addition, Grunwell et al. state at column 3, lines 58-62), "Additionally, the compounds of this invention readily undergo acid or base isomerization to the corresponding  $\Delta^4$ -steroids. Many of these 7( $\alpha,\beta$ )-loweralkyl-3-keto- $\Delta^4$ -steroids have recognized valuable biological properties, including...androgenic...[emphasis added]; and at column 9, lines 47-49, "The 3-keto-7-( $\alpha,\beta$ )-loweralkyl-androstane derivatives illustrated in formula I, wherein  $R_2$ ,  $R_3$ ,  $R_5$  and  $R_7$  are hydrogen, have anabolic and androgenic activity." [emphasis added]. Grunwell et al. disclose compounds which have agonist activity rather than antagonist activity.

In contrast thereto, the compounds of the present invention are antagonists. As taught by Example 180 of the present application, even when the compound of the present invention was added at a concentration of 10,000 nM/L, it exhibits no agonist action and is useful as an anti-androgenic agent. Example 180 also teaches that the development of androgen tolerance can be reduced by the compounds of the invention, page 422 line 8 to page 423, line 2.

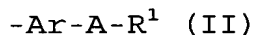
It is respectfully submitted that both the structure and the activities of the Grunwell et al. compounds are different from those of the present invention, and one skilled in the art reading Grunwell et al. would not be led to the compounds of the present invention.

Claims 1, 2, 5, 8, 11-13, 18, 19, 21 and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pierdet et al.

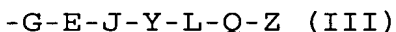
This rejection is respectfully traversed. Pierdet et al. only disclose compounds which are useful as haptenes and antigens. Pierdet et al. do not provide any working examples that demonstrate that any of their compounds can be used as an antiandrogenic agent, and, furthermore, there is nothing in Pierdet et al. that even suggests such utility for the compounds disclosed therein.

As explained above, the compounds of Pierdet et al. differ from those of the present invention even in terms of the steroid scaffold. Whereas the compounds of Pierdet et al. are unsaturated ketones, the compounds of the present invention are saturated ketones. Unsaturated ketones have different chemical properties from saturated ketones. In addition, the compounds of the present invention clearly differ from those of Pierdet et al. in the substituents at the 7-position. Pierdet et al. only disclose that the substituents is  $-(CH_2)_b-COOH$  or  $-N-O-(CH_2)_c-COOH$ , wherein b is a whole number from 1 to 18 and c is a whole number from 1 to 12. Both of these groups are characterized by a carboxyl group at the end of each group.

In contrast thereto, the compounds of the present invention have a characteristic substituent in the 7-position, namely, a substituent represented by formula (II):



wherein Ar represents a single bond or an aromatic hydrocarbon group, A represents a methylene group or  $-O-$ ,  $R^1$  represents a substituted alkyl group, a substituted alkenyl group, a substituted alkynyl group, and  $R^1$  is  $R^{1a}$  where  $R^{1a}$  is the general formula (III):



wherein G, E, J, Y, L, Q and Z are as defined in claim 2. These substituents would not have been contemplated by one skilled in the art reading Pierdet et al., as none of these substituents has a terminal carboxyl group.

Furthermore, when the process for synthesizing a compound of the present invention having a chained group in the 7-position is compared with a process for synthesizing a compounds disclosed by Pierdet et al., the processes are clearly different from each other. For example, Process V of the present invention at page 313, line 5 to page 316, line 11, is completely different from the process of Pierdet et al., column 6, line 27 to column 8, line 28.

It is respectfully submitted that one skilled in the art, reading the compounds of Pierdet et al., all of which have a methylene chain and a carboxyl group at the end as the substituent at the 7-position, would not be led to the compounds of the present invention, which have entirely different substituents at the 7-position.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

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Respectfully submitted,

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